Remitting narcolepsy? Longitudinal observations in a hypocretin-deficient cohort

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Abstract: Study Objective Narcolepsy type 1 (NT1) is considered a chronic, incurable disease. Excessive daytime sleepiness (EDS) is typically the most troublesome symptom, and more difficult to control by pharmacologic treatment than cataplexy. Although many NT1 patients are monitored by regular follow-ups, the purported relentless persistence of EDS has rarely been the object of longitudinal studies. Methods Retrospective analysis of 26 well-defined hypocretin-deficient NT1 patients who underwent longitudinal assessments of Epworth sleepiness scale (ESS) scores under stable pharmacotherapy. We present detailed case reports of four patients with unusual spontaneous improvement. Results Over a mean observation period of 5 years, changes in ESS scores between first and last examination were 4 points in 19 patients (73%). Three patients deteriorated by 5 points, four patients ameliorated by 7-11 points. Among the latter, subjective sleepiness resolved in all four patients, and three of them continued showing ESS scores <11 after cessation of their pharmacotherapy. Without therapy, two patients did not fulfill anymore the ICSD-3 multiple sleep latency test criteria (mean sleep latency >8 minutes), one of whom did not fall asleep during maintenance of wakefulness test. Multiple linear regression analysis identified higher cerebrospinal fluid (CSF) hypocretin level ($p < 0.001$) and absence of fragmented nighttime sleep ($p = 0.001$) as independent associates of EDS improvement. Conclusions The longitudinal course of NT1-related sleepiness is not invariably stable, but included spontaneous deterioration or improvement in 27%. Spontaneous improvement can persist after treatment discontinuation and resemble remission. Milder hypocretin deficiency and good nighttime sleep may predict a more favorable disease course.

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Remitting narcolepsy? Longitudinal observations in a hypocretin-deficient cohort

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Abstract

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Methods: Retrospective analysis of 26 well-defined hypocretin-deficient NT1 patients who underwent longitudinal assessments of Epworth sleepiness scale (ESS) scores under stable pharmacotherapy. We present detailed case reports of four patients with unusual spontaneous improvement.

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Conclusions: The longitudinal course of NT1-related sleepiness is not invariably stable, but included spontaneous deterioration or improvement in 27%. Spontaneous improvement can persist after treatment discontinuation and resemble remission. Milder hypocretin deficiency and good nighttime sleep may predict a more favorable disease course.

Statement of Significance

This study on longitudinal clinical evolution in narcolepsy type 1 (NT1) suggests that a significant minority of patients can improve spontaneously akin to clinical remission, and that measurable cerebrospinal fluid (CSF) hypocretin levels and consolidated nighttime sleep may constitute positive prognostic factors. Where available, repetitive measures of hypocretin demonstrated a progressive decline despite clinical improvement, indicating compensatory mechanisms distinct from the hypocretin system. These findings challenge the exclusive role of hypocretin deficiency in NT1 pathophysiology, question the classical view of NT1 as an incurable disease, and may stimulate new research on compensatory mechanisms. Moreover, a better characterization of patients with spontaneous improvement may have important prognostic and therapeutic implications.

Key words: narcolepsy; longitudinal; remission; CSF hypocretin level

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Introduction

The clinical course of narcolepsy type 1 (NT1) is classically considered as monophasic and non-remitting. The defining symptoms, excessive daytime sleepiness (EDS) and cataplexy, typically evolve acutely, although their onset may be separated by several months or even years [1]. Once established, both symptoms are thought to persist for a lifetime. This seems in accordance with the acute loss of >90% of hypocretin-producing neurons in the hypothalamus, causing irreversible hypocretin deficiency [2].

While this classical notion of a relentless persistence of NT1 symptoms has been widely accepted, its natural course has rarely been the object of longitudinal studies [1–4]. Few anecdotic reports [7] and therapeutic clinical trials seem to confirm long-term stability of EDS [8–11]. However, since many patients had changes in type and dosage of their pharmacotherapy during the observation period, it appears difficult to draw reliable conclusions on the natural evolution of symptoms. On the other hand, there is accumulating evidence for a more variable and dynamic disease course than traditionally assumed, especially at its onset. For instance, Pizza *et al.* [5] described in 21 drug-naïve children a heterogeneous natural evolution of NT1 symptoms with gradual changes in cataplexy phenomenology and sleep-wake behavior over a mean follow-up of 2.1 years. In the same line, a case description suggests that NT1 can evolve progressively over the years paralleled by declining cerebrospinal fluid (CSF) hypocretin levels [6]. Finally, while remission of symptoms has been noted to occur in patients diagnosed with NT2 and other hypersomnolence disorders [12, 13], such an unexpected disease course has not been described in NT1 patients [14].

Here, we retrospectively assessed the stability of EDS in well-defined hypocretin-deficient NT1 patients with constant therapy regimen over a mean observation period of 5 years. In addition, we present detailed case histories of NT1 patients with spontaneous improvement (n = 4), including sustained clinical remission (n = 3) that persisted after treatment withdrawal.

Methods

Inclusion criteria

We retrospectively evaluated 65 NT1 patients seen in the sleep clinic of the Department of Neurology, University Hospital Zurich, between 2004 and 2016. Inclusion criteria were a definite diagnosis of NT1 according to the ICSD-3 criteria (AASM 2014) [15] with proven CSF hypocretin deficiency (<200 pg/ml according to Zurich standards), and a longitudinal follow-up under stable NT1 treatment of at least 12 months. The flowchart in Figure 1 illustrates the number of patients that had to be excluded from the final analysis. Briefly, we first excluded patients without CSF hypocretin analysis (n = 6) or lack of informed consent (n = 2). Next, we excluded 21 patients with too short (<1 year) follow-up period at our department. We did not exclude 10 NT1 patients despite changing therapy regimen during the follow-up, but analyzed them separately. Eventually, we included 36 well-defined NT1 patients with follow-up over at least 1 year, including 26 patients with stable therapy regimen. The Ethics Committee of the Canton of Zurich, specialized subcommittee for Psychiatry, Neurology, Neurosurgery (BASEC No. 2017-00875), approved the study protocol.

Diagnostic work-up of participants

We retrieved detailed clinical information from the patients' medical records of the included 36 NT1 patients. Demographical characteristics comprised age, sex, body mass index (BMI). One patient was African, one was Asian, the remaining were Caucasians. Diagnostic work-up comprised in all patients a detailed interview (including information regarding cataplexy, sleep paralysis, hallucinations, nighttime sleep disturbances), 2-week actigraphy, video-polysomnography and multiple sleep latency test (MSLT), analyzed according to slightly modified standard criteria, as described in previous work [16, 17]. Epworth sleepiness scale (ESS) determined subjective daytime sleepiness. Baseline values of the Ullanlinna Narcolepsy Score [18] were available from all but two patients, and specific information were retrieved regarding cataplexy characteristics and frequency. All patients had definite cataplexy, and all had multiple sleep-onset rapid eye movement periods (SOREMPs) in their diagnostic MSLT. Human leukocyte antigen (HLA)-genotyping was available in 34 patients, all of them positive for the HLA-DQB1*0602 haplotype. CSF hypocretin levels were analyzed as previously described [19]. Decrease in CSF hypocretin levels was labeled as undetectable if <30 pg/ml, and low if between 30 and 200 pg/ml. At follow-up, we routinely assessed current medication and ESS scores as well as patient descriptions of changes in NT1 symptoms.

Observation period, outcome measures

For the main study population (n = 26), the duration of the observation period was determined by the documentation of a steady therapy regimen and available ESS scores. The observation period ended if patients had no further follow-up in our clinic or when pharmacotherapy had to be changed. Of note, in order to identify patients with spontaneous improvement, the observation period continued in case of treatment cessation. Primary outcome measure was the change in ESS score between baseline and last examination on the same treatment or after treatment cessation (Δ_{ESS}). Thus, ESS values assessed while the patient was still on therapy, or after therapy cessation, counted together. We considered ESS changes of >4 points as significant, which is in agreement with a recent longitudinal population-based study on daytime sleepiness [20]. Hence, we labeled a >4 point increase in ESS score as spontaneous deterioration, and a >4 point decrease as spontaneous improvement. We defined clinical remission as the absence of NT1 symptoms for at least 6 months after complete cessation of pharmacotherapy. In addition, we performed a sub-analysis in 10 patients with variable NT1 treatment. To this end, we compared the first available ESS score on any type of EDS treatment with the last one (per definition on another type of treatment), and applied the same criteria for judging the clinical course as mentioned above.

Statistical analysis

Statistical analyses were performed using SPSS (version 23). Group data were described by means and *SD*s. For normally distributed data, we applied Student's *t*-test. We used Pearson correlation to assess "longitudinal stability" of ESS scores in the patient group with $\Delta_{ESS} \leq 4$ points. The paired samples *t*-test was applied to compare longitudinal ESS scores. To identify

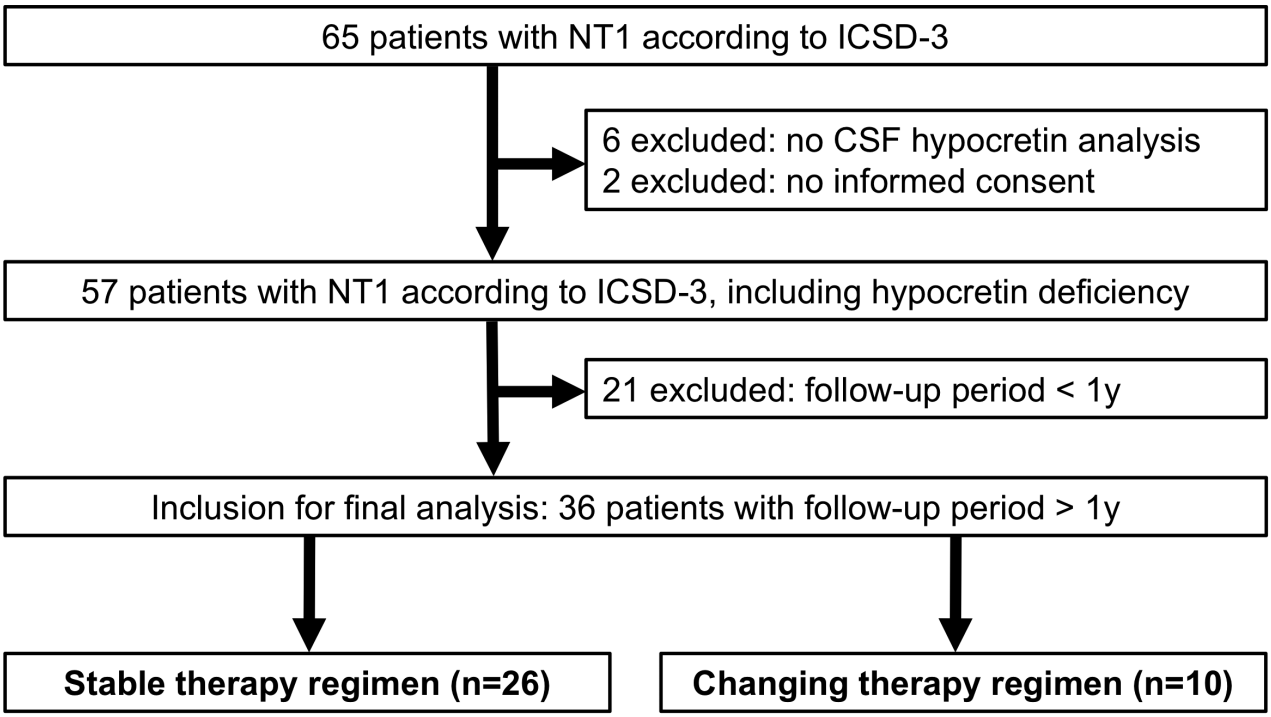

Figure 1. Overview of patient selection based on pre-defined inclusion criteria.

predictors of improving ESS scores, we used stepwise multiple regression analysis with the following independent variables: Gender, age of onset of EDS, delay between EDS onset and diagnosis of NT1, ESS at presentation, presence of hypnogogic hallucinations, sleep paralysis and disturbed nighttime sleep at presentation. Significance was accepted at $p < 0.05$.

Results

Longitudinal observation of 26 NT1 patients under stable therapy regimen

On average, the duration of the observational period was 5 ± 3 years (range: 1–12 years), and started with a latency of 13 ± 11 years (range: 1–44 years) after disease onset, and 9 ± 5 months (range: 2–26 months) after the last modification in pharmacotherapy. This lag between therapy adjustment and initiation of the observation period makes delayed treatment effects of stable pharmacotherapy, as observed for sodium oxybate [21], unlikely. During the observation period, changes in ESS scores were ≤4 points in 19 patients (73%, stable disease), whereas ESS scores increased by 5 points in three patients (12%, spontaneous deterioration) and decreased by 7–11 points in four patients (15%, spontaneous improvement). In the 19 patients with minor ESS changes, stability was reflected by a strong correlation between first and last ESS values ($r = 0.85$, $p < 0.001$). Table 1 shows the demographical and clinical characteristics of the three groups, as well as their pharmacotherapy during the observation period.

Correlates and predictors of sleepiness evolution

Positive changes (improvement) in ESS scores correlated with higher CSF hypocretin levels ($r = 0.66$, $p < 0.0005$; Figure 2A). ESS scores at the beginning of the observation period did not differ between NT1 patients with detectable and undetectable CSF hypocretin levels (14.3 ± 2.6 vs. 13.2 ± 4.3, $p = 0.53$). At the end, however, ESS scores appeared unchanged in patients with undetectable CSF hypocretin levels (14.4 ± 4.8), but significantly decreased in those with detectable CSF hypocretin levels (9.3 ± 4.9, $p = 0.033$) (Figure 2B).

Multiple linear regression analysis confirmed higher CSF hypocretin levels as independent associate of improving ESS scores (Table 2). In addition, absence of a complaint of disturbed nighttime sleep at baseline was independently associated with a more favorable evolution of ESS scores during the observation period.

Longitudinal observation of 10 NT1 patients with changing therapy regimen

Demographic and clinical data of the 10 patients with changing therapies (three females, seven males) were not different from the 26 patients with stable treatment. Four patients (40%) had detectable and six patients (60%) had undetectable CSF-hypocretin levels. Treatment changes were restricted to pharmacotherapy in eight patients, with one change in three patients and two changes in five patients (due to insufficient efficacy in 40%, insufficient tolerability in 40%, or for unclear reasons in 20%). Two further patients had comorbid severe obstructive sleep apnea with additional adjustments of apnea therapy (changes of ventilation parameters of continuous positive airway pressure therapy in both cases, multilevel surgery in one case, mandibular advancement orthesis in one case). When comparing the means of the first documented ESS score on any type of EDS-specific therapy (15.0 ± 3.8) with the last one (14.4 ± 4.5), no significant change was identified (–0.6 ± 2.6, $p > 0.05$; mean time period 6.6 years, range 1–15 years). Only

Table 1. Demographical and clinical characteristics of 26 NT1 patients with stable treatment

	Stable values in ESS score (≤4 points)	Deterioration in ESS score (≥5 points)	Improvement in ESS score (≥5 points)
N	19 (73%)	3 (12%)	4 (15%)
Disease onset to observational period, years	12 ± 7	21 ± 19	13 ± 21
Duration of observational period, years	4.7 ± 3.2	2.4 ± 1.0	7.1 ± 3.3
$\Delta_{ESS\ score}$ (range)	0.4 ± 2.1 (–2 to 4)	5.0	–8.8 ± 2.1 (–7 to –11)
Age at disease onset, years	24 ± 12	29 ± 19	28 ± 12
Female sex, *n*	12	1	2
Body mass index, kg/m^2	24.7 ± 5.0	28.2 ± 3.4	28.7 ± 3.5
CSF hypocretin level, pg/ml	14 ± 31	0.0	88 ± 53
Detectable CSF hypocretin, *n*	4	0	4
Treatment, *n*			
No pharmacotherapy	2	1	1
Sodium oxybate (GHB)	11	0	1
Stimulants (modafinil, methylphenidate)	12	1	2
Antidepressants	7	1	0
Clinical characteristics at presentation, *n*			
Hypnagogic/hypnopompic hallucinations	10	1	1
Sleep paralysis	12	1	2
Disturbed nighttime sleep	14	3	2
Cataplexy leading to falls	11	1	2
Cataplexy occurring at least daily	11	1	0
Cataplexy occurring at least weekly	6	0	3
Cataplexy occurring less often than weekly	2	1	0
No information on cataplexy available	0	1	1
Ullanlinna Narcolepsy Score	25 ± 6	23 ± 6	19 ± 1
Polysomnography findings at presentation			
Sleep efficiency (sleep time), %	83.6 ± 21	64.7 ± 33	90.5 ± 7
Arousal index, /hour	17.8 ± 21	9.5 ± 5.8	8.0 ± 5.8
Nocturnal SOREMP, *n*	8	2	1
MSLT findings at presentation			
Mean sleep latency, min	1.8 ± 1.2	1.7 ± 1.7	2.5 ± 1.0
Number of SOREMPs / number of naps	0.8 ± 0.2	0.5 ± 0.4	0.7 ± 0.2

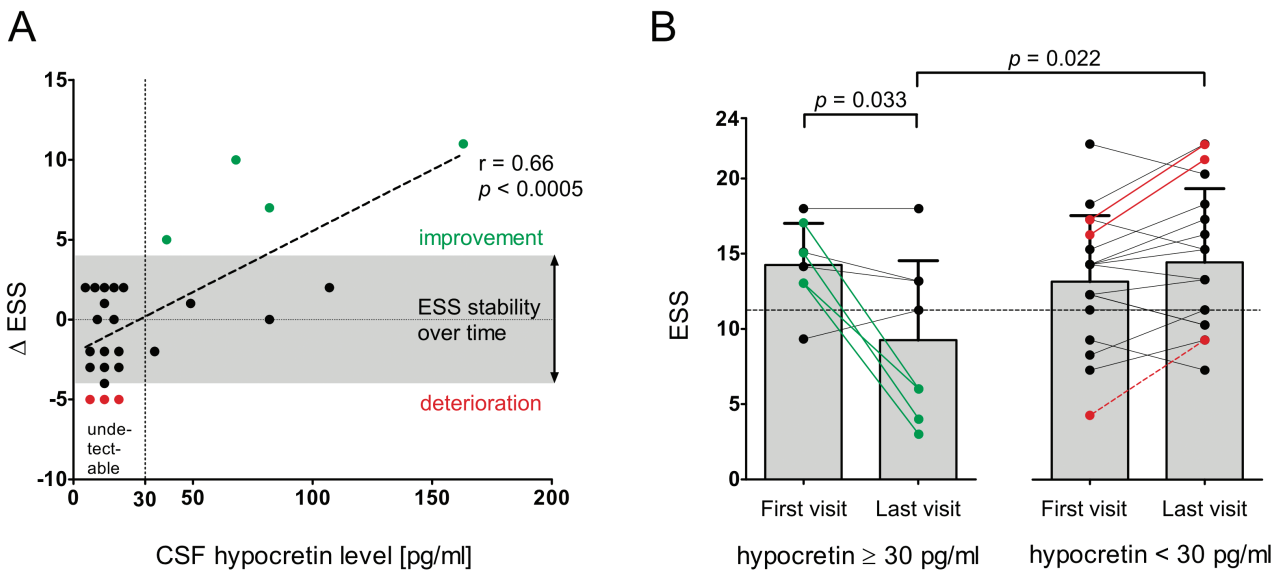

Figure 2. Impact of cerebrospinal fluid (CSF) hypocretin levels at presentation on the longitudinal disease course of narcolepsy type 1. (A) Pearson correlation of CSF hypocretin levels (pg/ml) and change of ESS scores during the observation period ($r = 0.66$, $p < 0.0005$). (B) Comparison of mean ESS values at first versus last visit of the observation period, both for patients with low CSF hypocretin values (≥30 pg/ml, left panel) and for patients with undetectable hypocretin values (<30 pg/ml, right panel). The dashed black line indicates the cut-off for a "normal" ESS score (<11 points). The boxes show mean and *SD*. Green dots indicate the four patients who improved by >4 ESS points, red dots indicate the three patients who deteriorated by >4 points in ESS (dashed line for patient whose ESS remained <11 points, i.e. within a physiological range), black dots indicate the 19 patients with stable disease as defined by minor changes in ESS scores ≤4 points.

Table 2. Multiple linear regression model for coefficients of changes in ESS scores during the observational period

Dependent variable	Significant coefficients	Estimated effect (β)	Standard error	*t*	*p*
$\Delta_{\text{ESS score}}$	CSF hypocretin level [pg/ml]	– 0.624	0.014	– 4.587	< 0.001
	Disturbed nocturnal sleep	0.507	1.471	3.726	0.001

Additional coefficients included in the model were age at presentation, age at disease onset, duration of observational period, latency between disease onset and observational period, body mass index, and mean sleep latency on MSLT.

one patient exhibited a significant decrease of the ESS score from 15 to 8 points during a follow-up period of 15 years, but this improvement occurred after the addition of sodium oxybate. The remaining nine patients showed minor ESS changes ≤4 points.

Assuming that all 10 patients with therapy change had probably a stable natural disease course, the distribution of various courses changes to stable disease in 81%, deterioration in 8% and improvement in 11% of patients of all 36 subjects under study.

Detailed presentation of four NT1 patients with spontaneous improvement/remission

Patient 1 (male) presented to our department at the age of 55 years. He described an acute onset of EDS and definite cataplexy, involving arms and legs but without falls, triggered by strong emotions, at age 15 years. He denied sleep paralysis, hypnagogic hallucinations and disturbed nighttime sleep, but reported episodes of automatic behavior during daytime. His EDS has caused several traffic accidents. CSF hypocretin level was 163 pg/ml, and he was found to carry the HLA-DQB1*06:02 gene (Figure 3). Polysomnography showed a sleep latency to N2 and R sleep of 4 minutes and 133 minutes, respectively, and a sleep efficiency of 82.4%. Mean sleep latency on MSLT was 3.0 minutes, with two SOREMPs (sequence of sleep stages: non-rapid eye movement sleep stage 1 - non-rapid eye movement sleep stage 2 - rapid eye movement sleep [N1-N2-R]). On 2-week actigraphy, there was no sign of an insufficient sleep syndrome or a circadian rhythm disorder (mean resting period 8 hours, stable circadian rhythm). Under regular modafinil treatment, ESS scores dropped from 22 to 18 points. Two years after treatment initiation, at the age of 57 years, he reported complete cessation of cataplexy. Given further improvement of EDS, he started taking modafinil only when driving long distances or attending important meetings. Nevertheless, ESS scores (without modafinil) gradually dropped in the following 10 years to 8 points. Thus, at the age of 67 years, he claimed to be cured from narcolepsy. At that point, repeated MWTs (carried out with modafinil as required by the road traffic-licensing department) had shown stable improvement. A follow-up MSLT performed in drug-free condition, revealed a mean sleep latency of 8.5 minutes and one SOREMP. The precedent 2-week actigraphy yielded similar results as the initial examination at presentation with a regular mean resting period of 7 hours 43 minutes and no signs of a circadian rhythm disorder. A follow-up lumbar puncture was performed showing a further decrease of CSF hypocretin levels to 121 pg/ml.

Patient 2 (male), presented in our clinic, aged 26 years, shortly after developing EDS and, 2 months later, cataplectic attacks that were triggered by laughter and involved his head and both legs, without causing falls. He denied sleep paralysis, disturbed nighttime sleep and hypnagogic hallucinations. His medical history was remarkable for severe traumatic brain injury at the age of 12 years. CSF hypocretin level was 68 pg/ml, and he was found to carry the HLA-DQB1*06:02 gene. Polysomnography showed a sleep latency to N2 and R sleep of 4 minutes and 0.5 minutes, respectively, and a sleep efficiency of 95.6%. Mean sleep latency on MSLT was 3.9 minutes, with three SOREMPs (sequence of sleep stages in two naps N1-R, in one nap N1-N2-R). The precedent 2-week actigraphy showed no signs of an insufficient sleep syndrome (mean resting period 7 hours 46 minutes) or a circadian rhythm disorder. After initiation of modafinil, ESS scores decreased from 13 to 4 points, and he was able to remain awake on MWT. Few months later, at the age of 27 years, modafinil had to be stopped because of side effects (nausea, palpitations), but sleepiness did not return. Furthermore, cataplexy ceased completely and the patient refused to take further medication, as he felt cured from narcolepsy. At follow-up examinations, always in drug-free conditions, ESS scores were <10 points, he could stay awake on MWT and the MSLT improved with a mean sleep latency of 10.1 minutes (with two SOREMPs). CSF hypocretin levels were undetectable in a second analysis at the age of 31 years.

Patient 3 (female), presented in our clinic at the age of 60 years and reported progressive onset of EDS since age 41, followed after 15 years by generalized cataplexy with secondary falls. She also suffered from daily hypnagogic hallucinations and fragmented nighttime sleep, but never experienced sleep paralysis. CSF hypocretin level was 82 pg/ml, and she was found to carry the HLA-DQB1*06:02 gene. Polysomnography showed a sleep latency to N2 and R sleep of 16 minutes and 75 minutes, respectively, and a sleep efficiency of 85.7%. She had episodes of somniloquia during R sleep, but muscle atonia during R sleep was otherwise preserved. Mean sleep latency on MSLT was 1.8 minutes, with four SOREMPs (sleep stage sequence N1-N2-R in three naps, N1-R in one nap). Her ability to stay awake on MWT was severely impaired, with unintended sleep occurring after a mean latency of 2.1 minutes. Under low-dose treatment with sodium oxybate (2 × 1.5 g), she reported marked consolidation of nocturnal sleep, reduction in cataplexy frequency from 2–3×/week to 1–2×/months, while hypnagogic hallucinations now occurred only once weekly. She also felt more alert during daytime, as documented by mild amelioration of both subjective and objective sleepiness measures. Seven years later, at the age of 67 years, the patient noticed a spontaneous improvement of all NT1 symptoms despite unchanged treatment with 2 × 1.5 g sodium oxybate. ESS score decreased to 6 points, she had no longer any cataplectic attacks and only very rarely hypnagogic hallucinations. There was also a substantial improvement of mean sleep latency on MWT to 35 minutes.

Patient 4 (female) is a refugee from Eritrea, who presented to our clinic at the age of 21 years. She described fever and flu-like symptoms during her escape through Sudan, and immediately afterwards developed EDS and generalized cataplectic attacks precipitated by strong emotions 2 years earlier, at the age of 19 years. CSF hypocretin level was 39 pg/ml, and she was

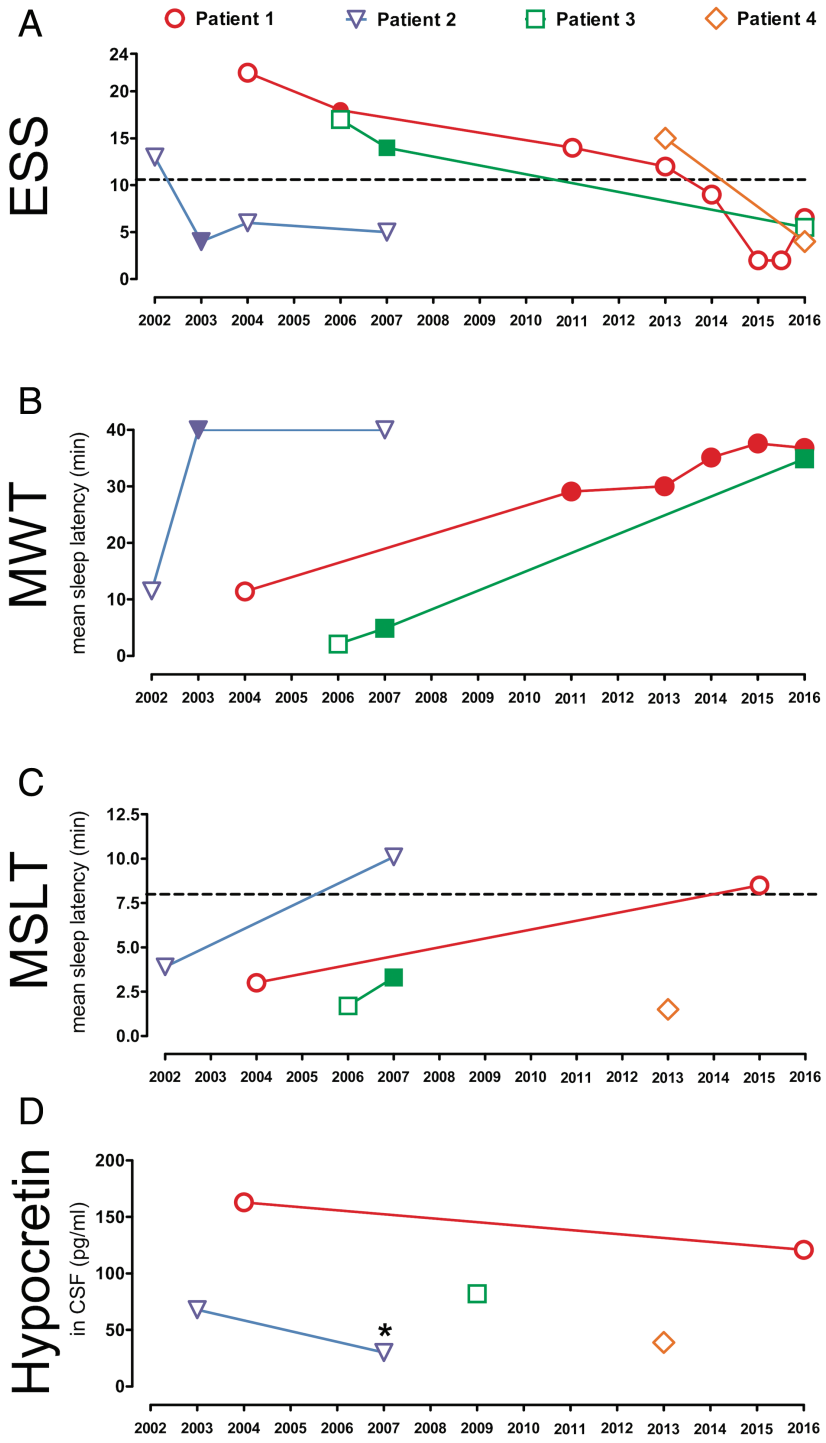

Figure 3. Overview of the longitudinal disease course of 4 patients with spontaneous improvement as assessed by (A) ESS, (B) MWT and (C) MSLT (cut-off for pathological sleepiness: mean sleep latency < 8 minutes). Panel (D) displays the concentration of hypocretin in the cerebrospinal fluid (CSF) over time. *hypocretin concentration unmeasurable (<30 pg/ml). Open symbols indicate examination without pharmacotherapy for narcolepsy; filled symbols indicate examination under the pharmacotherapy for narcolepsy. For patient 1, the MWT was carried out with modafinil medication (filled symbols), which was a requirement of the road traffic licensing department. Otherwise, he was drug-free in everyday life, reflected by open symbols for the ESS questionnaire and MSLT.

found to carry the HLA-DQB1*06:02 gene. She denied sleep paralysis, disturbed nighttime sleep or hypnagogic hallucinations. Polysomnography showed a sleep latency to N2 and R sleep of 1.6 minutes and 106 minutes, respectively, and a sleep efficiency of 98%. Mean sleep latency on MSLT was 1.5 minutes, with two SOREMPs (sleep stage sequence N1-N2-R). Because still breastfeeding, her treatment was limited to non-pharmacologic symptom management. In the following year, she reported a spontaneous improvement of EDS and cessation of cataplexy. She refused any pharmacotherapy, and felt cured from

narcolepsy. Her last recorded ESS score was 4 points at the age of 24 years. She does not have a driver's license.

Discussion

During the chronic disease phase, every fourth NT1 patient reported considerable changes in subjective sleepiness despite stable therapy regimen, including both deterioration ($n = 3$) and spontaneous improvement ($n = 4$). Most strikingly, three patients continued showing ESS scores <11 without pharmacotherapy, and improvement of sleepiness was paralleled by a normalized MSLT in two patients. Multiple regression analysis suggested milder CSF hypocretin deficiency and good nighttime sleep as predictors of spontaneous improvement in EDS. Interestingly, when repetitive CSF-hypocretin measurements were performed in two patients, we found a discrepancy between clinical amelioration and progressive hypocretin deficiency, which challenges the classical concept of hypocretin as the exclusive NT1 biomarker.

Although classified as chronic disease with stable course, "clinical stability" in NT1 has actually never been defined, and longitudinal data on symptom severity under steady therapy are rare. Our observation now suggests that sleepiness is indeed stable over the years in a majority of NT1 patients, as indicated by a strong Pearson correlation between first and last ESS values of 0.85. This number is identical to published data on test-retest reliability of the ESS in healthy subjects and patients with sleep apnea, also expressed by means of Pearson correlations [22]. Sure, our definition of long-term stability in NT1 can be criticized as purely academic, and the labeling of "deterioration" in three NT1 patients may appear inappropriate and without clinical relevance, possibly reflecting only physiological fluctuations of sleepiness rather than true exacerbation of the NT1 phenotype. Moreover, several other factors may aggravate (e.g. psychiatric comorbidities) or alleviate (e.g. behavioral coping strategies) NT1 symptoms.

The observation of spontaneous improvement akin to clinical remission, on the other hand, is more intriguing, and certainly of clinical interest. It cannot be downplayed to mere physiological fluctuations, because the changes were too pronounced and accompanied by remission of all other NT1 symptoms. Subjective sleepiness did not reemerge in two patients after withdrawal of their pharmacotherapy, and these patients eventually even claimed being cured. Without any pharmacotherapy, two patients had a mean sleep latency on MSLT of >8 minutes, one of whom remained wake during an entire 4 × 40 minutes maintenance of wakefulness test (MWT). Finally, the identification of milder hypocretin deficiency and undisturbed nighttime sleep in patients with favorable evolution points to an association of this unusual disease course with differential clinical and neurobiological features.

In view of a ~10% frequency in the present cohort, marked improvement of EDS and other NT1 symptoms may not represent an exceptional finding, and similar cases could show up in other sleep centers with sufficiently large NT1 patient cohorts. In the absence of published accounts, our observation provides the opportunity to speculate about its pathophysiological, therapeutic, and diagnostic implications. From a pathophysiology perspective, it is tempting to link the observed spontaneous improvement with the emerging concept that sleep-wake-regulating nuclei possess a potential of neuroplasticity, as indicated by increased numbers of histaminergic tuberomammillary neurons in NT1 brains [23–25], and elevated blood levels of brain-derived neurotrophic factor (BDNF) in NT1 patients [26–28]. In this context, our finding of progressive hypocretin deficiency in two patients suggests compensation mechanisms distinct from the hypocretin system, which warrants further studies.

As a potential explanation for the favorable disease course in patients with measurable hypocretin levels, higher numbers of surviving hypocretin neurons may more effectively compensate for their reduced signaling, hypothetically by reinforcing synaptic strength to other target nuclei involved in sleep-wake regulation (e.g. histamine). The likelihood that this putative neuroplastic adaptation has clinical impact might be higher when hypocretin neurons are destroyed in a slowly progressive manner, as was the case in two of our patients with follow-up CSF hypocretin measurements. A similar case was recently reported by Lopez *et al*. [29], describing a 17-year old NT1 patient with CSF hypocretin level of 106 pg/ml 1 year after the onset of sleepiness and partial cataplexy, with remission of cataplexy within 2 years despite further decrease of CSF hypocretin level to 27 pg/ml. These observations thus expand the meaning of detectable CSF hypocretin levels in NT1, which has already been linked to longer mean sleep latencies on MSLT [30], and less fragmented nighttime sleep [31].

From a therapeutic perspective, it has been argued that immunotherapy, when administered in close relationship to disease onset, can interrupt, delay or even reverse the destroying process of the hypocretin neurons [32, 33]. Future studies must evaluate whether NT1 patients with detectable CSF hypocretin levels—both with and without spontaneous clinical improvement—may still benefit from immunotherapy when given many years after disease onset. Increased recognition of this NT1 subgroup is warranted yet challenging, because detectable CSF hypocretin levels have been identified as predictor of a longer diagnostic delay [34, 35].

This work has several limitations. In addition to its retrospective design and small number of included NT1 patients, we must acknowledge that we did not perform urinary drug screening during MSLT/MWT and, hence, may have missed underhand consumption of psychostimulants, with the intention to avoid social/work-related restrictions or being banned from driving [36]. Second, although the employed radioimmunoassay kit for hypocretin-1 has a low inter- and intra-assay variability [19, 37, 38], its accuracy might be less reliable when CSF hypocretin levels are below 60 pg/ml, and the applied CSF hypocretin detection limit of 30 pg/ml might thus appear as too low. However, the identification of milder CSF hypocretin deficiency as an independent predictor of EDS improvement seems to justify such a low detection level and suggests that undetectable and very low CSF hypocretin levels possess differential clinical and prognostic value. In addition, another study in NT1 patients observed significant hypocretin-dependent differences in sleep fragmentation when using the same CSF hypocretin detection level of 30 pg/ml [31]. Third, by including only patients with stable therapy we could have introduced a selection bias, neglecting patients requiring frequent therapy modifications. Thus, our results cannot be generalized to all NT1 patients, and we might have overestimated the number of patients with spontaneous improvement. Finally, some of the patients revealed atypical features such as high sleep efficiency or long R sleep latency on polysomnography. These findings may raise suspicion about the

diagnosis of NT1, but all patients were diagnosed with positive hypocretin, HLA and MSLT criteria. It seems, however, possible that these patients somehow reflect an alternative phenotype of NT1.

In conclusion, spontaneous improvement akin to clinical remission—a hitherto almost unthinkable scenario in NT1 patients, though representing a well-known feature in many other autoimmune disorders of the nervous system—seems to occur in a minority of NT1 patients. NT1 patients with detectable CSF hypocretin levels and non-fragmented nocturnal sleep might constitute a target subgroup with differential prognosis and therapeutic requirements. Thus, our observation raises some hope that the natural course of NT1 may not be as adamantly persistent we believed as yet. Replication in a prospective study with a larger number of patients is warranted, ideally applying novel tools to better monitor the disease course both subjectively (e.g. with validated questionnaires reflecting the whole range of NT1 symptoms [39]) and objectively (e.g. with laboratory-based cataplexy documentation [40]).

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Notes

Conflict of interest statement. None declared.

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